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Severe adverse drug reaction in SARS-CoV-2 infection: AGEP induced by ceftriaxone and confirmed by patch test

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Adverse drug reactions (ADRs) are rarely reported in patients with coronavirus disease 2019 (COVID-19) despite the wide range of medications administered to slow the progression of the disease and relieve symptoms caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Recently, an overview of cutaneous ADRs by the most frequently used drugs in patients with COVID-19 highlighted antimalarials, antivirals, and anti-inflammatory drugs, but not antibiotics.[1,2] Only rare cases of drug-induced acute generalized exanthematous pustulosis (AGEP) due to hydroxychloroquine[3] and cephalosporins[4,5] have been reported in patients with COVID-19, but in none of these cases were patch tests (PTs) performed.

The article has not been published previously and is not currently submitted elsewhere.

CASE REPORT

During the first wave of COVID-19 in Italy, a 73-year-old woman with no history of drug allergies was admitted to our COVID-19 Unit with a 2-day history of fever (temperature 39°C), vomiting, and oxygen desaturation with breath sounds diminished bilaterally. Chest computed tomography revealed bilateral ground-glass opacities, and oxygen and intravenous ceftriaxone (2 g) was immediately started. After a swab for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was positive, ceftriaxone was replaced with azithromycin (500 mg/day); hydroxychloroquine (400 mg/day), antiretroviral therapy with darunavir/cobicistat (800/150 mg/day), and enoxaparin (4000 UI/day) were added because of deterioration of the patient's clinical conditions. On day 5 azithromycin was discontinued. Therapy was implemented with dexamethasone from day 8 to day 10 for

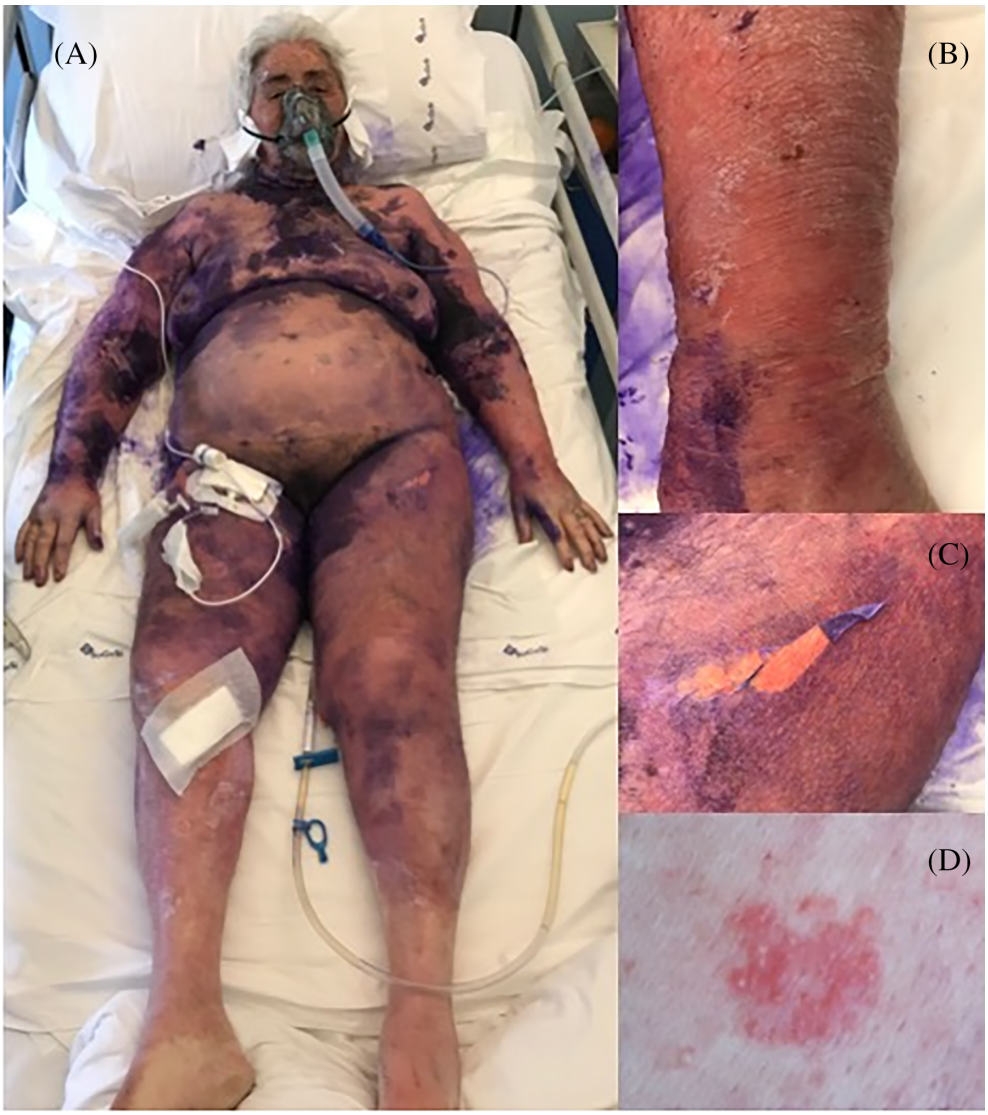

FIGURE 1 (A) Extensive erythematous eruption with (B) flaccid superficial pustules resembling blisters and (C) superficial detachment. (D) Positive patch test (++) with a pustular reaction pattern to ceftriaxone (5% in pet., D4)

progressive respiratory failure; on day 18, hydroxychloroquine and darunavir/cobicistat were also discontinued. On day 24, a high spiking fever (temperature 39.5°C) appeared and the patient received again intravenous ceftriaxone (2 g). One day later an extensive non-follicular pustular eruption on an erythematous base (60% of body surface area) appeared. Ceftriaxone was immediately discontinued and skin biopsy was performed revealing spongiform subcorneal pustules with edema of the papillary dermis; blood tests showed leukocytosis (16 700 per mm^3) with absolute neutrophilia (14 910 per mm^3). According to clinical and laboratory data, AGEP was diagnosed. The skin eruption in 2 days evolved into flaccid superficial pustules resembling blisters, rapidly denuding the skin superficial to the flaccid pustules, which affected 35% of the body surface area (Figure 1A–C), and this was associated with erosive conjunctival and oral involvement. Due to the worsening of her condition, the patient was transferred to the intensive care unit. Evaluation by reverse transcriptase-polymerase chain reaction for SARS-CoV-2 from the skin blister fluid was negative. Supportive and intravenous immunoglobulin therapy (2.4 g/kg over 3 days) was administered with gradual improvement of skin and mucous lesions. Systemic and cutaneous clinical course was positive, the respiratory condition recovered, and re-epithelialization occurred in 3 weeks without scarring.

According to the initial clinical picture and based on the EUROSCAR scoring system, definite AGEP with a final score of 9 (morphology 6: pustules, 2; erythema, 2; distribution, 2; and course 0: mucosal involvement, −2; acute onset, 0; fever, 1; neutrophils, 1; skin histology, 3) in a patient with COVID-19 was diagnosed.

Three months after complete healing, patch test with ceftriaxone sodium 5% and hydroxychloroquine 10%, both in pet., were performed. Patch tests were occluded for 2 days with the Haye's Test Chambers (Haye's Service, Alphen aan den Rijn, The Netherlands) on Soffix tape (Artsana, Grandate, Italy), and readings were performed on day (D)2, D4, and D7.[5] On D2 and D4 a strong positive reaction (++) to ceftriaxone was documented with infiltrated erythema and pustules (Figure 1D).[6] The patient refused patch test biopsy.

DISCUSSION

To the best of our knowledge, this is the first case of severe cutaneous ADR in a patient with COVID-19 patient confirmed by patch test. The diagnostic value and safety of in vivo testing to investigate severe T cell–mediated hypersensitivities is still controversial. In fact, patch testing has been performed safely in AGEP, Drug Reaction with Eosinophilia and Systemic Symptoms, and Stevens-Johnson Syndrome-Toxic Epidermal Necrolysis,[7] whereas intradermal testing and provocation test in these severe ADRs are contraindicated.[8] We emphasize that in our patient patch testing with ceftriaxone showed a pustular reaction pattern, supporting the ability of the testing to reproduce the original ADR clinical pattern.

Chronology (fast elicitation in 1 day after reintroduction), elicitor, neutrophilia, positive pustular patch testing, and uncomplicated recovery of the patient pointed to an AGEP. As recently stated by the European Academy of Allergy Clinical Immunology position paper classification of cutaneous manifestations of drug hypersensitivity,[9] the large very superficial detachment observed in our patient resulted from confluent pustules resembling blisters.

The culprit drugs of AGEP are beta-lactam antibiotics, macrolides, diltiazem, terbinafine, and hydroxychloroquine.[9] In our patient, despite the large number of administered drugs, we performed a patch test with ceftriaxone for short latency time after its second administration and with hydroxychloroquine for its documented role in AGEP.[3,9] Patch test confirmed ceftriaxone as the culprit, but unfortunately we could not perform ultra-structural studies on ceftriaxone positive patch test biopsy to confirm the immunopathogenesis of AGEP, usually classified as a type IVd hypersensitivity reaction.[10]

In conclusion, given the plethora of used drugs and the lack of approved therapies for patients with COVID-19, our report underscores the necessity to identify culprit drugs in ADRs in these patients and confirms the value and safety of patch tests.

CONFLICTS OF INTEREST

All authors have no conflicts of interests to report.

AUTHOR CONTRIBUTIONS

Luca Stingeni: Conceptualization; data curation; investigation; methodology; supervision; visualization; writing-original draft; writing-review & editing. **Daniela Francisci:** Conceptualization; data curation; investigation; supervision; visualization; writing-original draft; writing-review & editing. **Leonardo Bianchi:** Conceptualization; data curation; investigation; methodology; supervision; visualization; writing-original draft; writing-review & editing. **Katharina Hansel:** Conceptualization; data curation; investigation; methodology; supervision; visualization; writing-original draft; writing-review & editing. **Marta Tramontana:** Conceptualization; data curation; investigation; methodology; supervision; visualization; writing-original draft; writing-review & editing. **Francesco Di Candilo:** Conceptualization; data curation; investigation; methodology; supervision; visualization; writing-original draft; writing-review & editing. **Massimo Mannarino:** Conceptualization; data curation; investigation; methodology; supervision; visualization; writing-original draft; writing-review & editing. **Matteo Pirro:** Conceptualization; data curation; investigation; methodology; supervision; visualization; writing-original draft; writing-review & editing.

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